Demystifying Medicine Series

Premature and Unusual Causes of Coronary Heart Disease

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NO Disclosures

No financial interests or relationships with a commercial entity

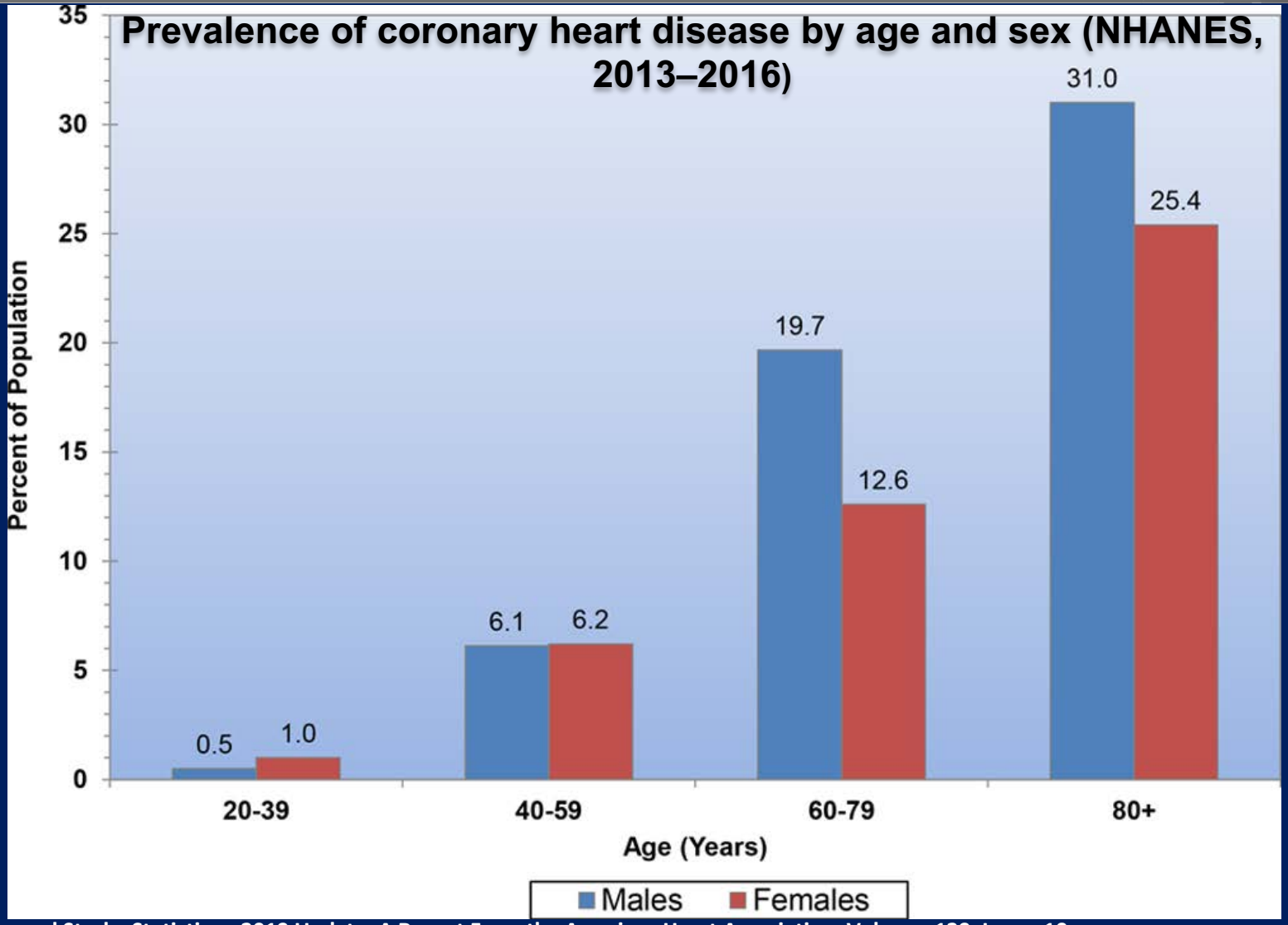
List of Non-FDA Approved uses

- None

Objectives

1. Discuss the pathophysiology of myocardial ischemia (angina)
2. Discuss the treatment of myocardial ischemia (angina)
3. Describe genetic approaches and characterization of molecular mechanisms involved in premature CAD.

Premature and Unusual Causes of Coronary Heart Disease



Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association, Volume: 139, Issue: 10, Pages: e56-e66, DOI: (10.1161/CIR.0000000000000659)

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Premature and Unusual Causes of Coronary Heart Disease

- 18.2 million Americans have CAD
  - White males > black males
  - Black females > white female
  - Hispanics slightly less than whites
  - Asians lowest
- 805,000 Americans have MI/year
- 0.5 million Americans die annually from CAD
  - Of those 0.5 million, 0.35 million die suddenly
- Annual cost: ~$190 billion*/year

- * 2015

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Myocardial ischemia is secondary to:

myocardial O_2 demand > myocardial O_2 supply

or

myocardial O_2 supply ≠ myocardial O_2 demand

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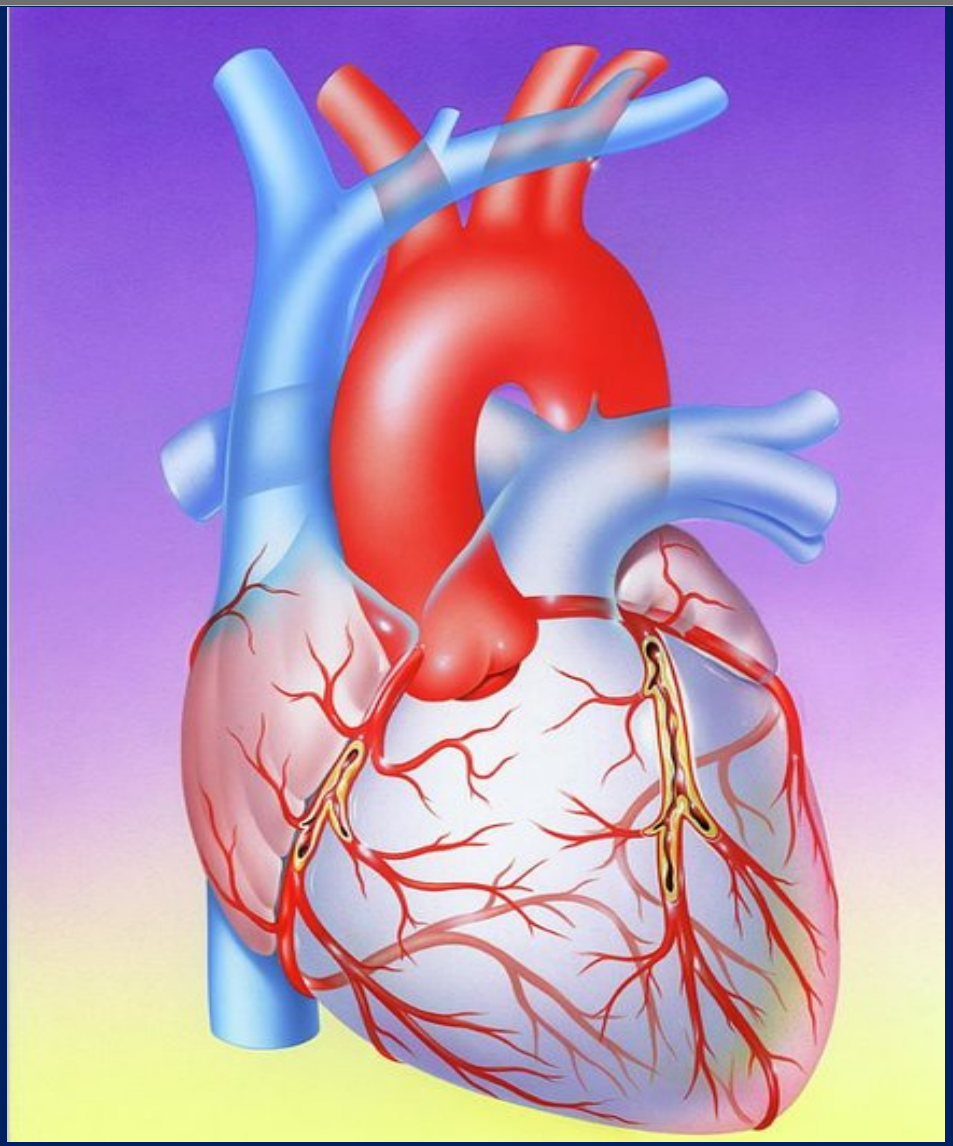

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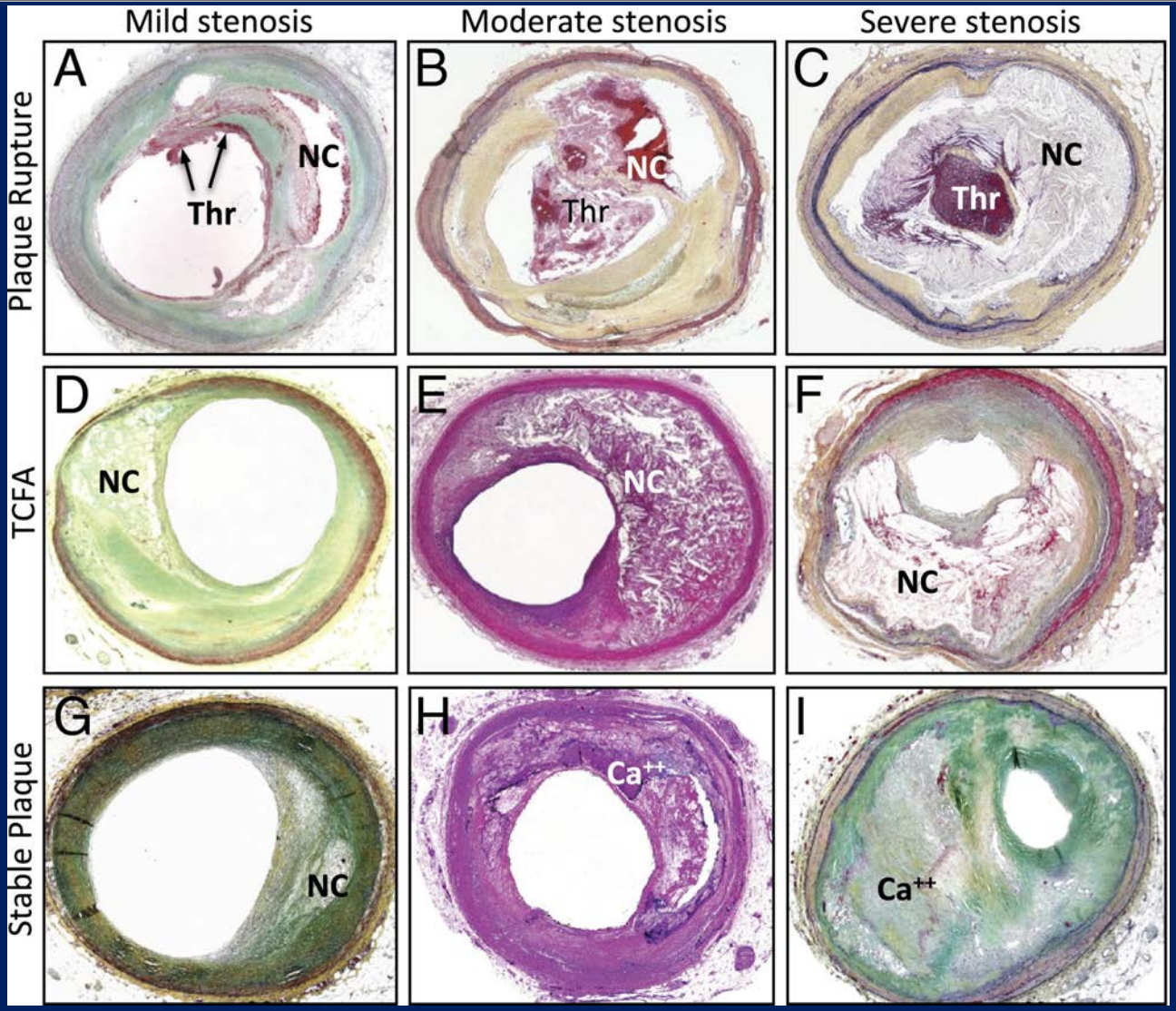

JACC.2013;61(10):1044-51

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Premature and Unusual Causes of Coronary Heart Disease

Case Presentation

- 29-year-old Caucasian man first developed exertional angina while serving in the U.S. Army in May 2009 **at age 19.**
- CAD risk factors:
  - 7 pack year smoker, d/c 2014 (also smokeless tobacco)
  - Father with PCI age 36, CABG age 49
  - Paternal grandmother with CABG age 46 (deceased)
  - 27-year-old brother alive and well without CAD (confirmed by LHC)

CAD Risk Factors

ENVIRONMENTAL RISK FACTORS

- Smoking
- High Fat Diet
- Lack of Exercise

OTHER RISKS

- Age & Gender
- Inflammation (HSCRP)

HERITABLE/GENETIC RISK FACTORS

- LDL
- Hypertension
- Diabetes type II
- Family history premature atherosclerosis
- Low HDL
- High triglycerides
- Homocysteine
- Progeria syndromes

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Premature and Unusual Causes of Coronary Heart Disease

"Inadequate Knowledge

Although much has been learned about the causes of coronary heart disease, the gaps in knowledge are noteworthy; for example, fully half of all patients with this condition do not have any of the established coronary risk factors (hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, and physical inactivity)."

Braunwald E. Shattuck lecture. NEJM. 1997;337:1360-69.

"…it is also important to consider that in data from the United Kingdom Heart Disease Prevention Project and other cohorts, approximately half of all patients suffering a CHD event have no established risk factors."

Hennekens CH. Circulation. 1998;97:1095-1102.

Premature and Unusual Causes of Coronary Heart Disease

Unanswered Questions

1. What is the risk factor or mechanism for the development of atherothrombotic disease in 10-20% of patients without identifiable risk factor or just age as risk
2. Many people with risk factor(s) have no apparent atherothrombotic disease
3. Why did this 19 y/o with a couple of risk factors possibly have CAD?

Hypotheses

1. Genetic basis – susceptibility genes (marker on chromosome 9p21)
2. Inflammation

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Case Presentation cont.

- Nuclear stress test in June 2009
  - Reached Stage 5, (17 METs), 85% target heart rate
  - Baseline ECG with ST depression with T-wave inversion in III/V5/V6.
  - Mildly dilated LV cavity
  - LVEF 48%
- Fixed inferior defect, no definite ischemia

- Lipid panel in December 2009: TC 177, LDL 111, **HDL 35**, TG 155

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Case Presentation cont.

- Diagnosed with anxiety/panic disorder as cause of chest pain and treated with anti-anxiety medication
- Continued to have exertional chest pain and separated from the Army in 2011 for medical reasons and enrolled in college
- July 22, 2014 awoke with terrible chest pain, dyspnea and diaphoresis. Attempted to walk 2 blocks to morning class and collapsed.
- Cardiac catheterization
  - Taken to University of Minnesota Medical Center and had LHC which revealed severe 3 vessel CAD

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- Angiogram

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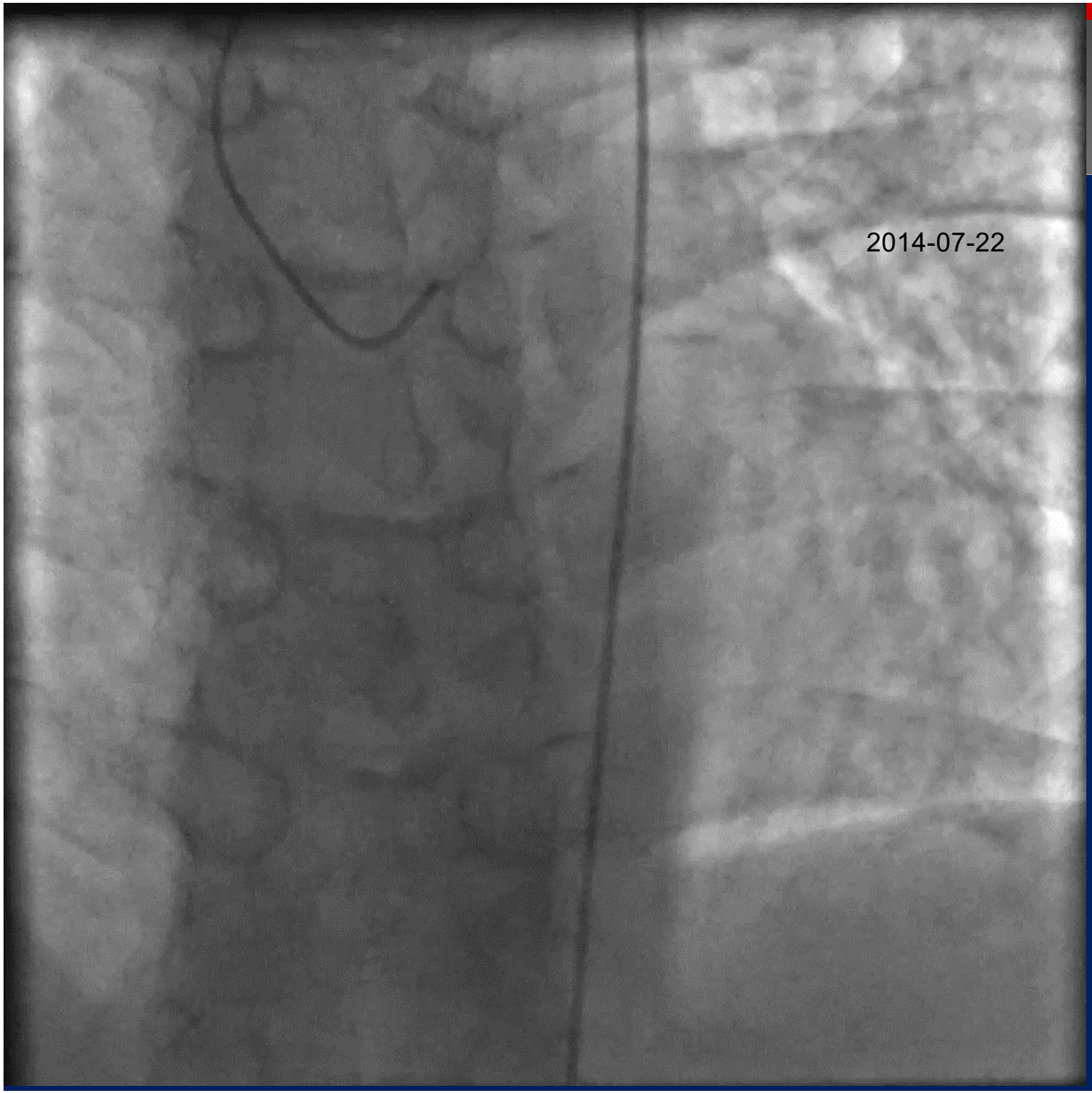

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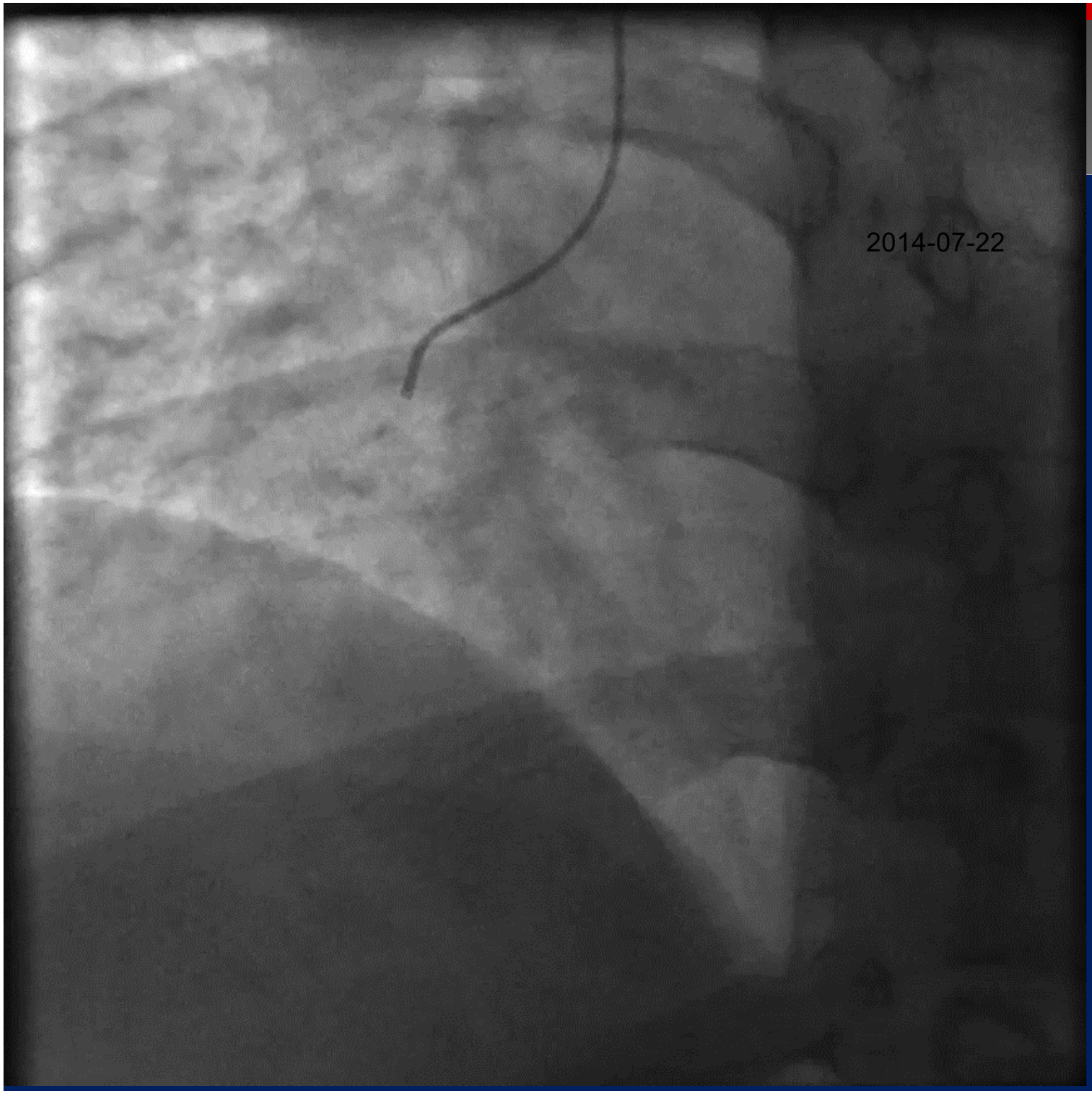

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Case Presentation cont.

- Underwent rescue angioplasty of the ramus and placed on an intraaortic balloon pump and then underwent emergent 4 vessel CABG:
  - LIMA -> LAD
  - SVG -> ramus
  - Free RIMA from hood of ramus vein graft -> 1st diagonal
  - SVG -> PDA
- Discharged on ASA 325 mg, atorvastatin 10 mg, metoprolol 25 mg bid, lisinopril 2.5 mg

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Case Presentation cont.

- Continued to have chest pain after CABG
- To ED September 9, 2014 with chest pain and catheterization on September 10th showed:
  - 70% ostial occlusion SVG-> ramus
  - 100% occlusion SVG-> PDA
  - LIMA/RIMA patent
  - Native LAD/RCA mid-vessel chronic total occlusion
  - Ramus with mild, diffuse disease
  - PCI to native RCA attempted without success

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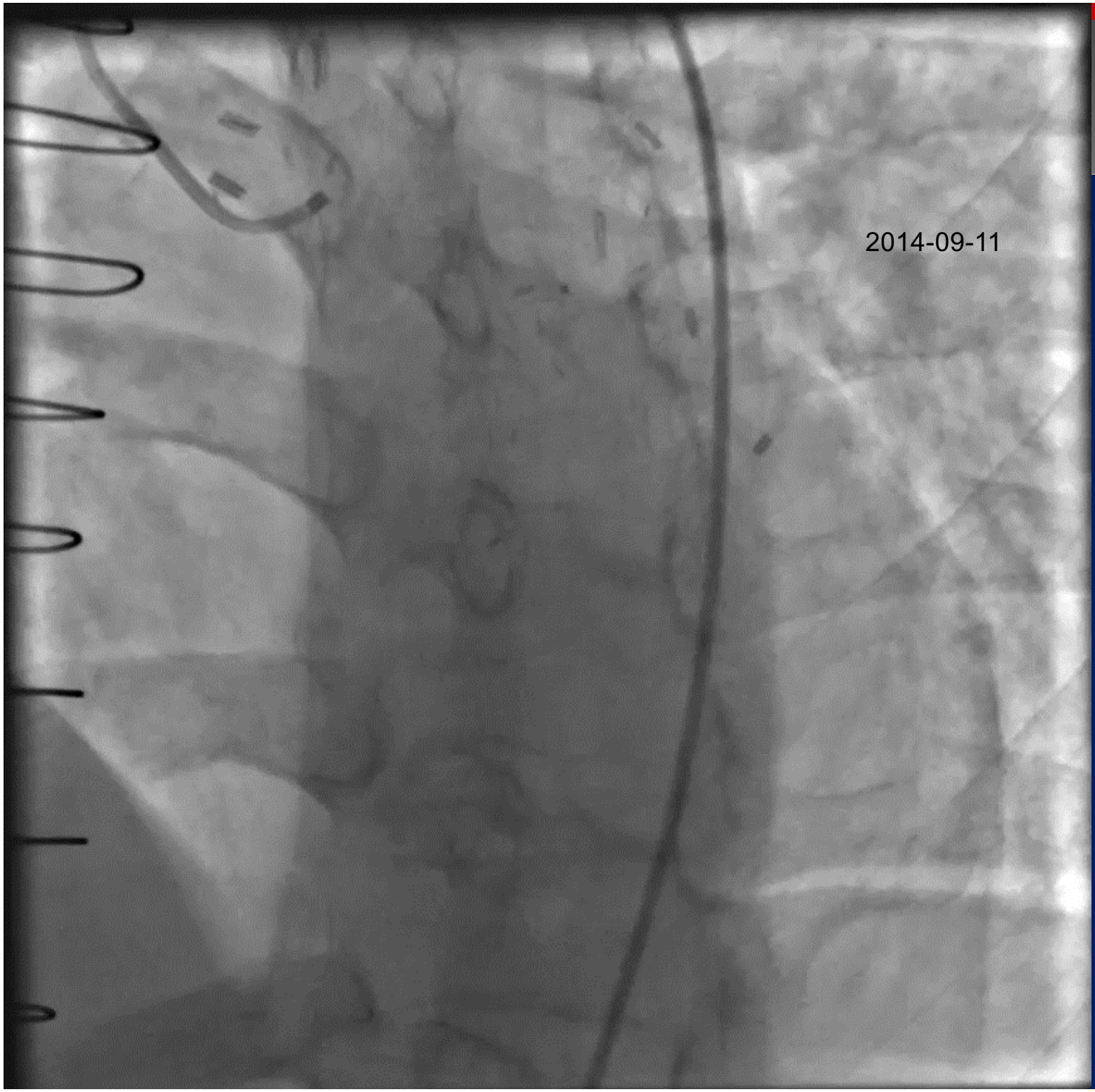

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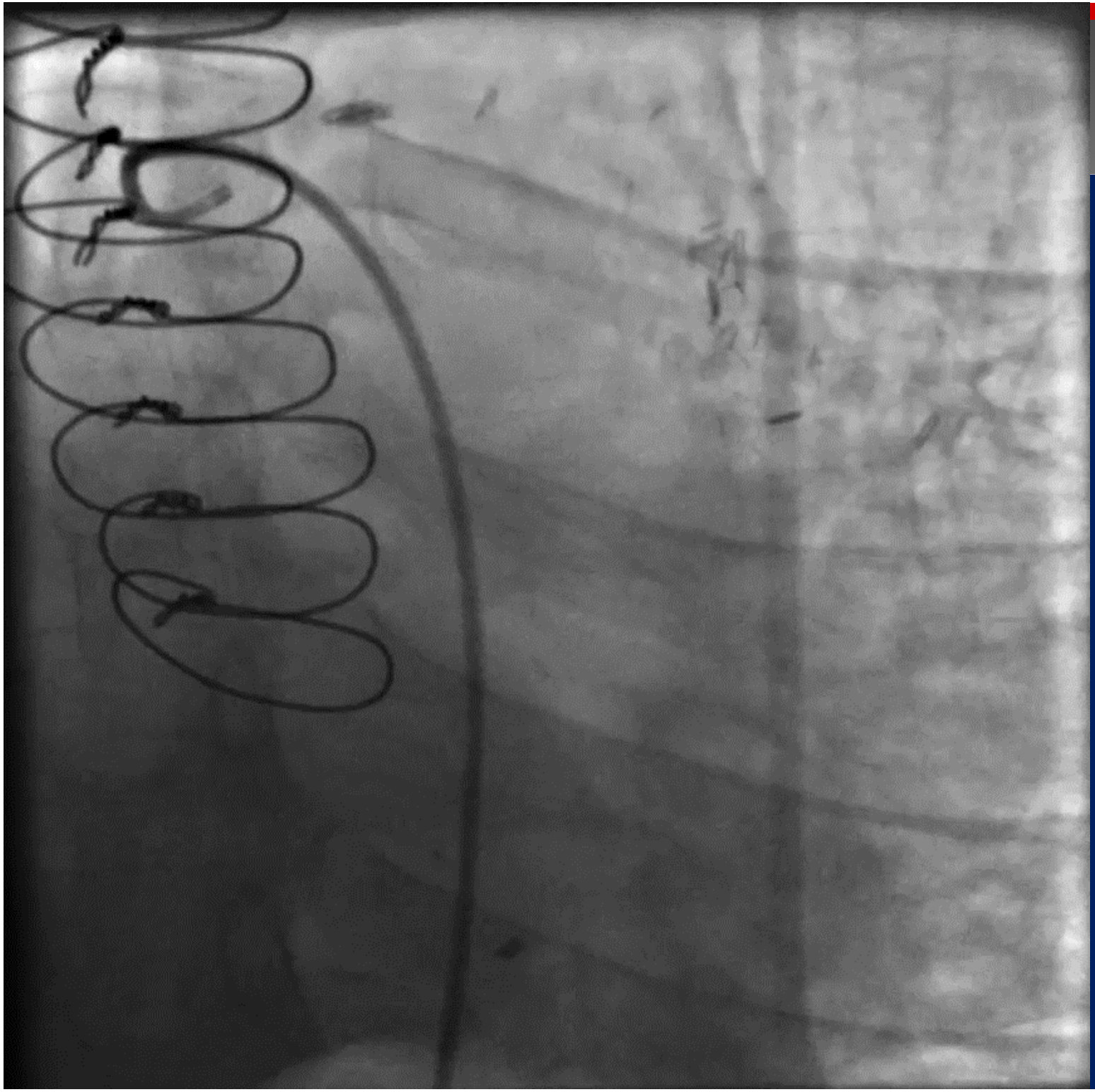

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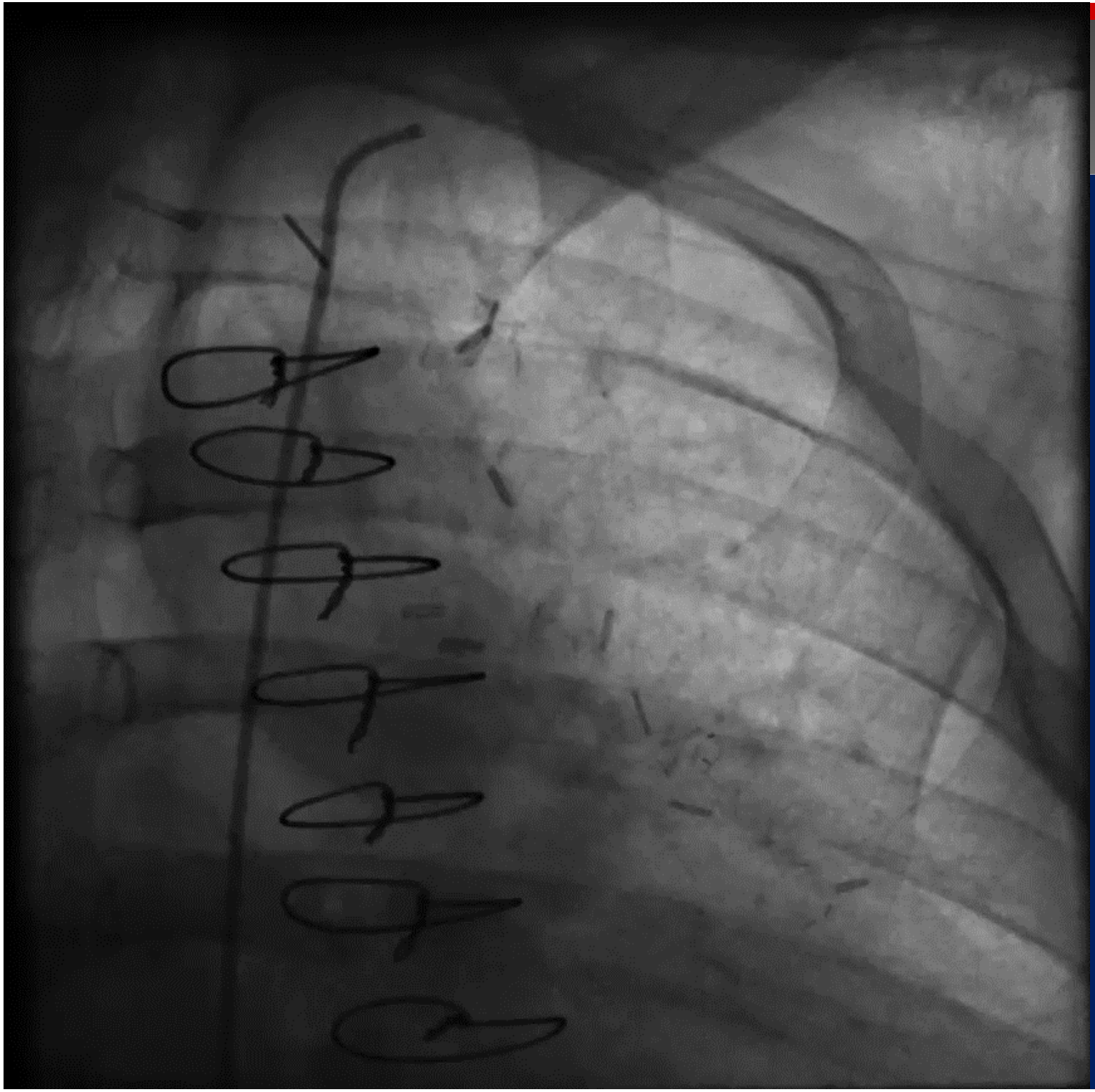

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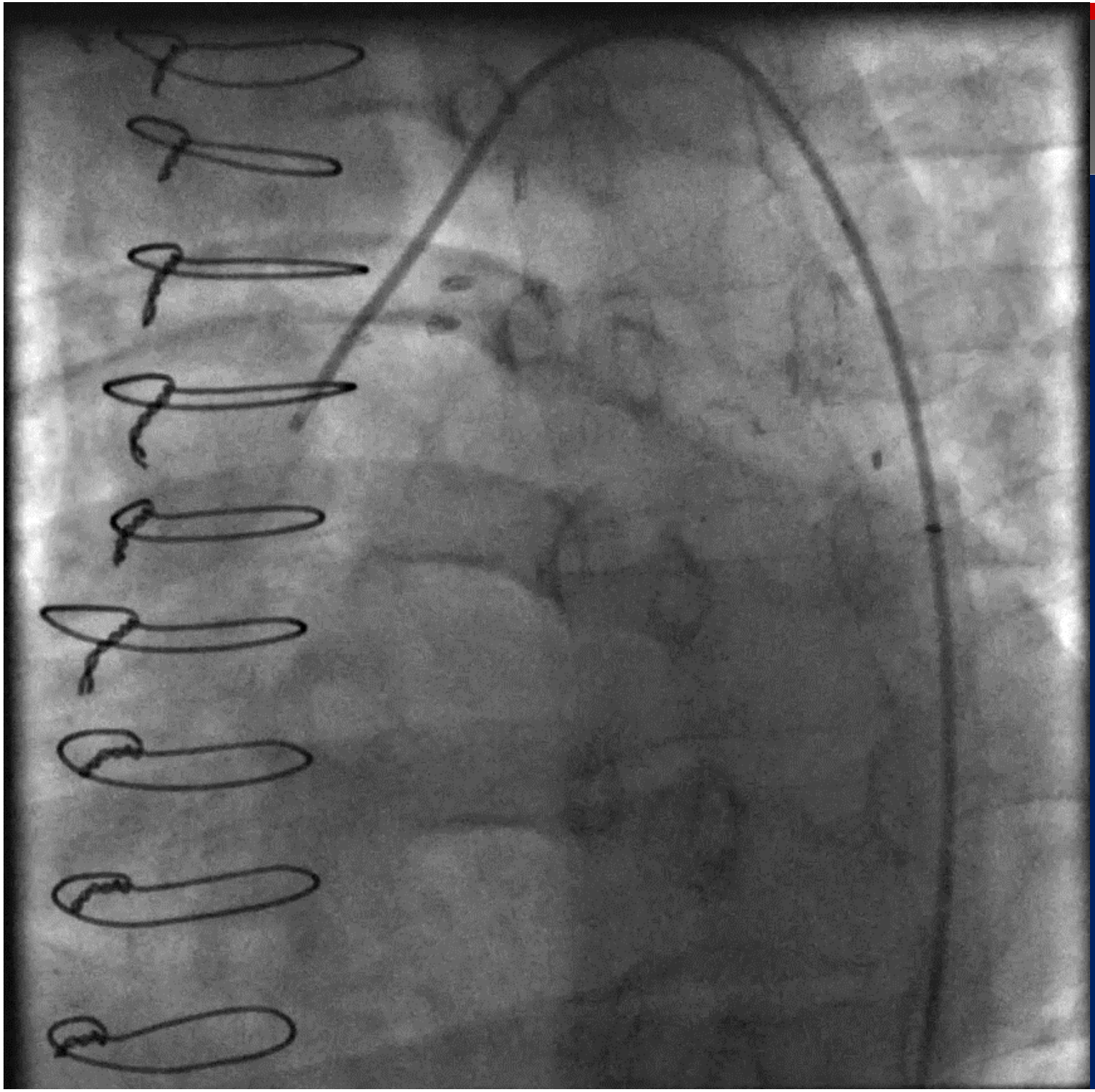

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Case Presentation cont.

- Discharged on ticagrelor 90 mg bid, isosorbide mononitrate 60 mg, atorvastatin 80 mg, ASA 81 mg, metoprolol tartrate 25 mg bid
- Brought back September 19, 2014 to try again
  - 2 Xience drug eluting stents (DES) to OM1
  - 2 Xience DES to ostial and mid-RCA
  - Unsuccessful attempt of PCI to distal RCA
  - Chest pain continues…..

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Case Presentation cont.

- Evaluated at the Cleveland Clinic in December 2014
  - Nuclear stress test done. Achieved 10 METS with mild chest pain. Scar in RCA territory but no active ischemia.
  - Echocardiogram revealed normal LVEF and no valve disease or wall motion abnormality.
  - Normal coagulation workup/HSCRP/ESR, negative ANCA's.
- Chest pain continues…..

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Case Presentation cont.

- Moved back home to Lima, Ohio to live with parents. Hospitalized February 22, 2015 for unstable angina. LHC revealed:
  - Distal RCA chronic total occlusion
  - 95% proximal stenosis of marginal branch
  - Subtotal stenosis septal perforator branch
- Returned to catheterization laboratory on 2/27/15 for planned interventions.
  - Angioplasty of proximal RCA
  - Stent to marginal branch

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Case Presentation cont.

- Chest pain continues….
  - Hospitalized in April and May for chest pain requiring IV nitroglycerin
- June 2015, seen at NIH for first time

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Stress Cardiac MRI (06/19/2015)

Segment #	Rest Function	Viability	Stress Function	Rest Perfusion	Stress Perfusion
LAD Territory					
1. Basal Anterior	Normal	26-50% Hyperenhanced	Normal	Normal	Normal
2. Basal AnteroSeptal	Normal	Normal	Normal	Normal	Severe subendocardial
7. Mid Anterior	Normal	Normal	Normal	Normal	Normal
8. Mid Anteroseptal	Normal	Normal	Normal	Normal	Severe subendocardial
13. Apical Anterior	Normal	Normal	Normal	Normal	Normal
14. Apical Septal	Normal	Normal	Normal	Normal	Severe transmural
17. Apex	Normal	Normal	Normal		
RCA Territory					
3. Basal Inferoseptal	Normal	26-50% Hyperenhanced	Normal	Normal	Severe transmural
4. Basal Inferior	Akinetic	> 75% Hyperenhanced	No change	Severe transmural	Severe transmural
9. Mid Inferoseptal	Normal	26-50% Hyperenhanced	Normal	Normal	Severe subendocardial
10. Mid Inferior	Hypokinetic	> 75% Hyperenhanced	No change	Severe subendocardial	Severe transmural
15. Apical Inferior	Normal	26-50% Hyperenhanced	Normal	Normal	Moderate subendocardial
Circumflex Territory					
5. Basal Inferolateral	Aneurysmal	51-75% Hyperenhanced	No change	Severe transmural	Moderate transmural
6. Basal Anterolateral	Normal	26-50% Hyperenhanced	Normal	Normal	Normal
11. Mid Inferolateral	Normal	26-50% Hyperenhanced	Normal	Normal	Moderate transmural
12. Mid Anterolateral	Normal	< 25% Hyperenhanced	Normal	Normal	Normal
16. Apical Lateral	Normal	Normal	Normal	Normal	Normal

Notes: N. A. = not assessed; Hyper = hyperenhanced which generally correlates with infarction but can be abnormal in other conditions such as myocarditis; Possible perfusion defects have low probability of significant stenosis.

LVEF 49%

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- 8/2017 – 3 stents placed in his LAD

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Stress Cardiac MRI (11/15/2017)

Segment #	Rest Function	LGE Imaging	Stress Function	Rest Perfusion	Stress Perfusion
LAD Territory					
1.Basal Anterior	Hypokinetic	1-25%		Normal	Normal
2.Basal Anteroseptal	Normal	Normal		Normal	Normal
7.Mid Anterior	Hypokinetic	Normal		Normal	Normal
8.Mid Anteroseptal	Normal	Normal		Normal	Normal
13.Apical Anterior	Normal	Normal		Normal	Normal
14.Apical Septal	Normal	Normal		Normal	Normal
17.Apex	Normal	Normal		Not Done	Not Done
RCA Territory					
3.Basal Inferoseptal	Normal	26-50%		Moderate Subendo	Moderate Subendo
4.Basal Inferior	Akinetic	76-99%		Severe Transmural	Severe Transmural
9.Mid Inferoseptal	Normal	Normal		Normal	Normal
10.Mid Inferior	Hypokinetic	26-50%		Moderate Subendo	Severe Subendo
15.Apical Inferior	Normal	1-25%		Normal	Normal
Circumflex Territory					
5.Basal Inferolateral	Akinetic	1-25%		Moderate Subendo	Mild Subendo
6.Basal Anterolateral	Hypokinetic	1-25%		Normal	Normal
11.Mid Inferolateral	Akinetic	51-75%		Normal	Normal
12.Mid Anterolateral	Hypokinetic	Normal		Normal	Normal
16.Apical Lateral	Normal	Normal		Normal	Normal

LVEF 46%

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Medical Management of CAD

- Nitrates - dilate blood vessels = reduce BP, improve blood flow to ischemic tissues
- Beta blockers – reduce HR & contractility
- Calcium channel blockers – dilate arteries, (reduce contractility, reduce HR), improve blood flow to ischemic tissues
- Partial FA oxidation (PFox) inhibitor & blocks late Na current (ranolazine) – glucose metabolism uses less O_2, reduction of the intracellular sodium and calcium overload in ischemic cardiac myocytes

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Medical Management of CAD cont.

- ACE-I/ARB - reduce BP, inhibit progression?
- Statins - inhibit plaque progression, plaque stabilization, reduced inflammation, reversal of endothelial dysfunction, and decreased thrombogenicity
- Anti-platelet treatment – inhibit platelet activation

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Revascularization

- Percutaneous coronary intervention (PCI)
- Coronary artery bypass graft surgery (CABG)

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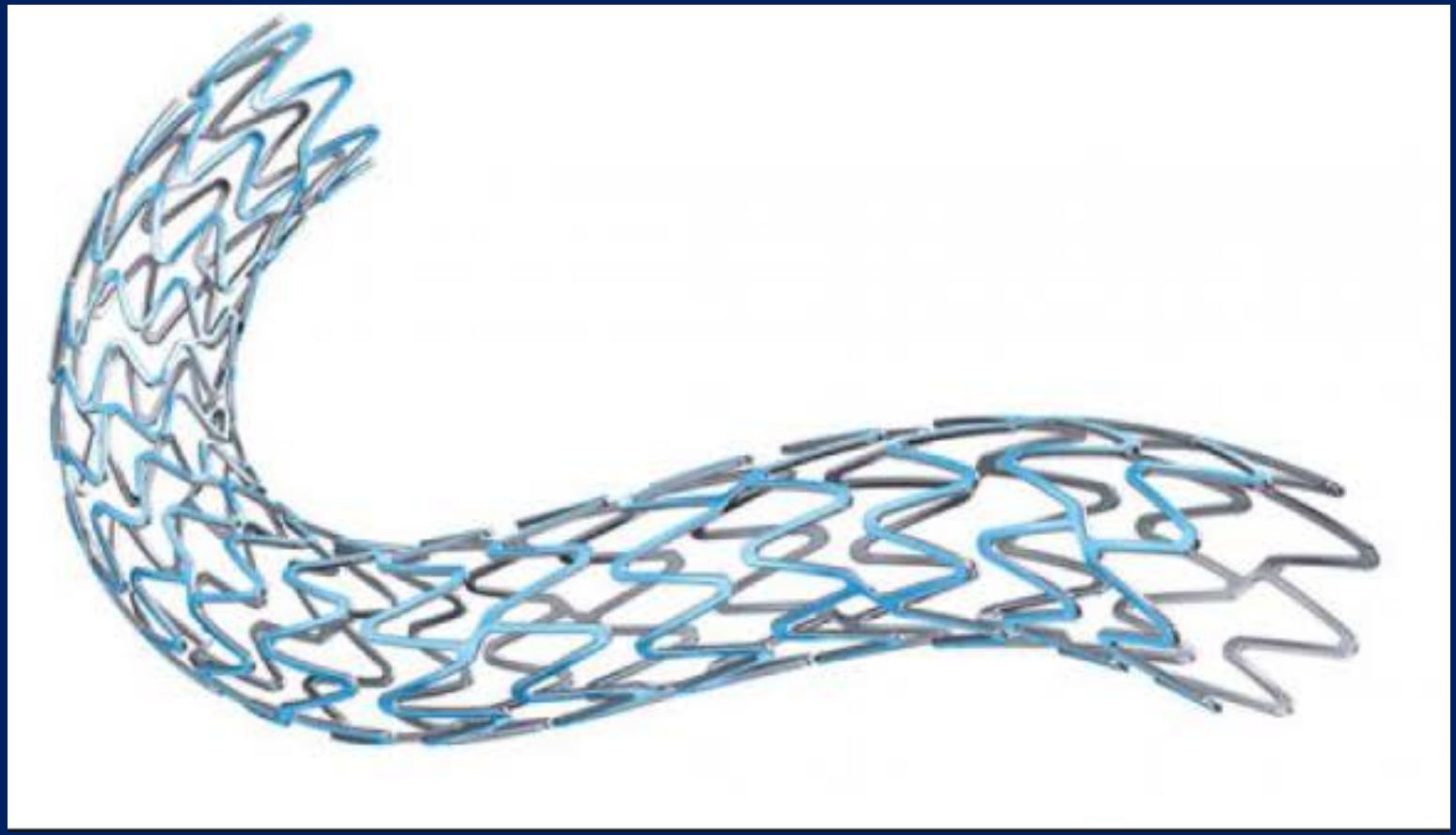
Drug Eluting Stent



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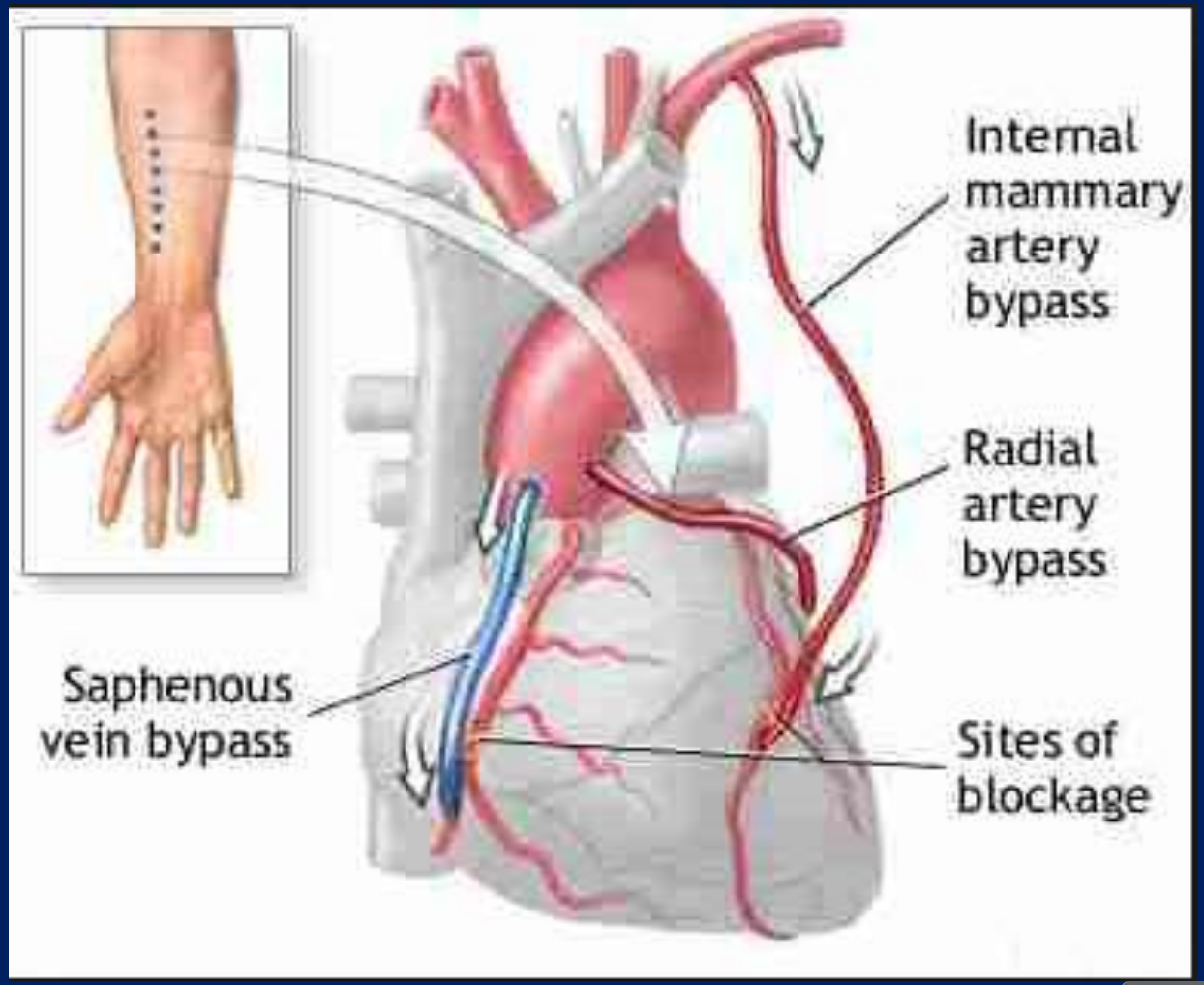
Coronary Artery Bypass Surgery



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Alternative Therapies for Refractory Angina

1. **External counterpulsation** — External counterpulsation (ECP), also referred to as enhanced external counterpulsation (EECP), is a technique that increases arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation). Cuffs are wrapped around the patient's calves, thighs, and pelvis and, using compressed air, sequential pressure (up to 300 mm Hg) is applied in early diastole to propel blood back to the heart.
   - The mechanism of these benefits is not clear, but is probably related, at least in part, to improvements in stress-induced myocardial perfusion, left ventricular diastolic filling, peripheral arterial flow-mediated dilation, and endothelial function.

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Alternative Therapies for Refractory Angina cont.

2. Spinal cord stimulation
3. Transmyocardial laser revascularization (TMR)
4. Coronary sinus reducing device
5. Apheresis
6. Multiple medications
   - Inhibition of fatty acid oxidation (trimetazidine, perhexiline)
   - Nicorandil, allopurinol
   - Ivabradine
7. Heart transplantation

Case Presentation cont. - Treatment

- Medications:

Lisinopril 5 mg QD
Clopidogrel 75 mg QD
Metoprolol succinate 50 mg QD
Ranolazine 1 gm 2x/day
Atorvastatin 80 mg QD
Isosorbide mononitrate 120 mg QD

Aspirin 81 mg QD
Spironolactone 12.5 mg QD
Furosemide 20 mg PRN
Allopurinol 400 mg QD
Famotidine 20 mg QD

Perhexaline considered

External counterpulsation initiated.

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Case Presentation cont.

- Imaging Studies:
    1. Total body CT angiogram – unremarkable except for calcification in the wall of the descending aorta
    2. PET/CT – no vascular uptake
    3. Echocardiogram - The left ventricle is normal in size. The LV systolic function is mildly decreased with a calculated EF of 49%. The mid and basal Inferior, inferoseptal and mid inferolateral segments are thin and akinetic. Hyperdynamic contractility of remaining walls. Abnormal LV relaxation is present.

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Case Presentation cont. (4/15/2019)

- Chest pain and TNG use unchanged
- Lipid Profile: Chol 125, HDL 37, LDL 54, TG 168
  - Apolipoprotein A-1 124 (104-202)
  - Apolipoprotein B 64 (66-113)
- HSCRP: 0.3
- ProBNP: 81 (0-124)
- Echocardiogram: no change
- Stress CMR: no change

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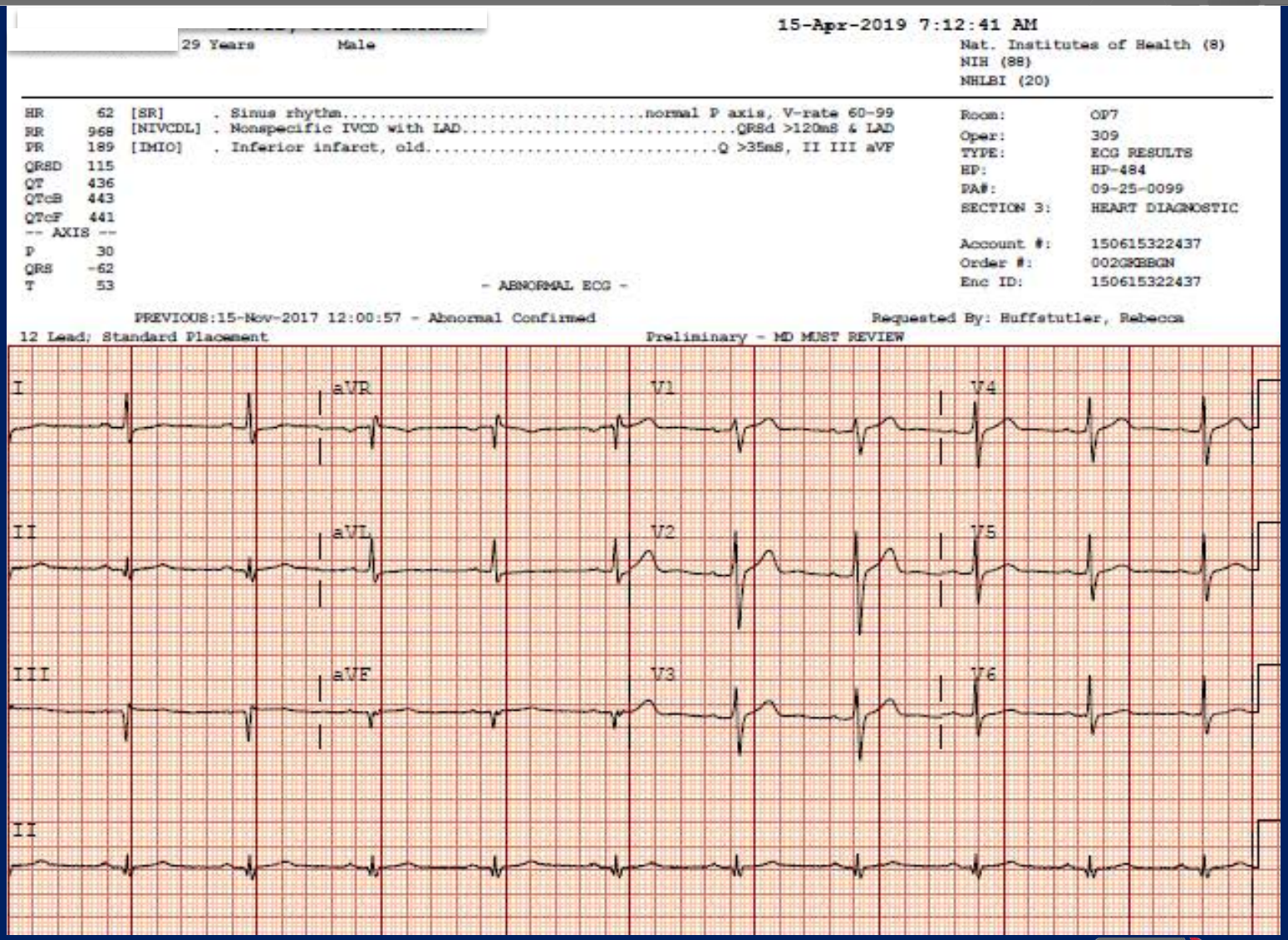

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Case Presentation cont.

Treadmill Exercise Test (04/16/2019):

1. Started with 4-5/10 chest pain which slowly increased during the test
2. Able to reach stage 3 of the Bruce protocol (9.6 METs) when termoinated due to 8/10 chest pain
3. TNG little benefit post test with pain returning to baseline 17:23 into recovery
4. No ECG changes during test
5. One ventriocular ectopic during test

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Case Presentation cont. Summary

- 14 catheterizations and 23 stents later, from which he often received transient relief, still complains of chronic chest pain exacerbated by exertion.
  - Sublingual nitroglycerin only 1-2x/week
- Anatomy and functional testing unchanged
- Referred for heart transplantation
  - Turned down because risks > benefits
  - Questioned noncardiac etiology of chest pain

Premature and Unusual Causes of Coronary Heart Disease

General Summary

1. Despite great progress in the diagnosis, understanding of the pathophysiology, and treatment of atherothrombotic coronary artery disease, there are still significant gaps in each area. Therefore we would benefit by:
   - Better understanding of the importance of already identified risk factors such as inflammation, adiposity, the nitric oxide system, genes, homocysteine, hormones, etc. as well as yet unidentified risk factors
     - Differentiating between a marker and an etiologic factor

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General Summary cont.

2. Better understanding and subsequent more aggressive therapy for diabetes, dyslipidemia, hypertension and smoking cessation.
3. Improved vascular delivery systems, devices to open and maintain patency of vessels, and vascular imaging systems
4. Improved surgical access, operative techniques, anti-clotting agents, and conduits

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Coronary Artery Disease